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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,498	02/15/2000	HANS-PETER SCHWARZ	BHV-314.01	8060

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,498	SCHWARZ ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,35-37,39-41,43,44,64-66,68,69 and 72-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32,39,40,43,44,64,65,68,69 and 72-76* is/are rejected.

7)☒ Claim(s) *35-37,41 and 66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Amendment filed July 12, 2004 has been entered. Claims 1-30, 33-34, 38, 42, 45-63, 67, and 70-71 are cancelled. Claims 31-32, 35-37, 39-41, 43-44, 64-66, 68-69, 72-78 are pending and have been considered on the merits in this Office Action.

Rejections Withdrawn

The rejection of Claims 31-32, 35-37, 39-40, 43-44, 66-69 and new Claims 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995) is withdrawn in light of the amendment . Burnouf-Radosevich et al. does not teach that there is at least 10 nM of the vWF propeptide in the composition disclosed therein.

Rejections Maintained

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 31-32, 39-40, 43-44, 64-65, 72, and 74-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Takagi et al. (Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6).

The rejection is maintained for reasons cited in the previous Office Actions. Applicants' argument that the claimed compositions are distinguished from Takagi et al.

because the Takagi et al. compositions are prepared from human platelets which "can potentially" be contaminated with viruses has been considered but is not deemed persuasive because Applicants have not provided any evidence that the platelets used in Takagi et al. were contaminated with viruses; especially the specific viruses that would be removed or inactivated by the step in the claims. Thus, there is no evidence of any patentable difference between the Takagi et al. preparation and that claimed. Likewise, Applicants argument that composition of Claim 72 is distinguished from Takagi et al. because the Takagi et al. preparation was not prepared under "scrupulous" conditions does not indicate how the Takagi et al. compositions is different from the composition claimed and does not provide any evidence that the Takagi et al. preparation is patentably distinguishable from that claimed. Takagi et al. disclose a composition comprising vWF propolypeptide isolated from human platelets (see p, 6017, Experimental Procedures). Since the vWF propolypeptide is a glycoprotein isolated from platelets it is considered a platelet glycoprotein component (clms 39-40). The purified vWF propolypeptide of Takagi et al. appears to be 95% pure (see SDS-PAGE gel in Fig. 1). The concentration of the vWF propolypeptide preparations disclosed in Takagi et al. were greater than 50 nM (see Fig. 4).

The present claims are drawn to a product-by-process. As evidenced by the prior art, it appears that the vWF propolypeptide was very well known in the art at the time of the invention. While the vWF propolypeptide composition of the prior art appears to have been made by a process different than that claimed, the vWF propolypeptide known in the art is identical in structure and function to the presently

claimed polypeptide and would inherently have the same properties and utilities as the polypeptide presently claimed. Applicants are reminded that something which is old does not become patentable upon the discovery of a new use. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) (see MPEP 2112). As explained in the previous rejection, the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). In the present case, there is no evidence and no reason to believe that the Takagi et al. purified preparation of pp-vWF contains contaminated active viruses. .

In the present case, it appears that the claimed compositions are patentably indistinguishable from the prior art, absent evidence to the contrary. In the alternative, the claimed compositions would be obvious over the prior art as described below.

Claim Rejections - 35 USC § 103

Claims 31, 32, 39, 40, 43, 44, 64, 65, 72, and new Claims 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-6020) in view of EP 0 131 740 (cited in IDS of Paper No. 20), Blann et al. (Eur. J. Vasc. Surg. (1994) 8 : 10-15; cited in IDS) and Applicants admissions in the instant Specification.

The claims are rejected for reasons stated in the previous Office Actions.

As admitted in the Specification (p. 4, last paragraph), the purification of pp-vWF and virus removal or inactivation (p. 7, first paragraph) were very well known processes at the time of the invention. Therefore, the present issue at hand is whether or not one of ordinary skill in the art at the time of the invention would have been motivated to combine these well-known methods to make the claimed product.

Applicants argue that there is no motivation to combine the cited references because there is no evidence that would enable one to conclude that high vWF levels were a potential cause of arterial disease and because Blann et al. indicates that further investigation was needed to understand the association between high vWF levels and diseases such as atherosclerosis.

These arguments have been considered but are not deemed persuasive for the following reasons:

Contrary to Applicants assertions, Blann et al. does provide suggestion that vWF is a causal factor in various types of atherosclerosis. First, Blann et al. emphasizes that vWF levels are raised in patients with atherosclerosis or related diseases (see

paragraph bridging p. 12-13). Secondly, Blann et al. repeatedly suggests that high levels of vWF might predispose to or promote atherosclerosis (p. 13, 1st Col. Middle and last paragraph) and that reducing vWF levels might be a future therapeutic approach (p. 13, last paragraph). Applicants imply that Blann et al. concludes that there is no data in humans that would allow conclusion that low vWF levels protect from atherosclerosis. However, when the citation is read in its entirety and with the knowledge of the teachings of Takagi et al., this statement does not imply that Blann et al. concludes that vWF is not a causative factor. Blann et al. merely states that due to the complexity of von Willebrand disease and due to the added complexity of its treatment with vWF and factors that induce vWF release, von Willebrand disease cannot be used as a model for low vWF. Moreover, Takagi et al. teaches that pp-vWF is also low in patients with von Willebrand disease (p. 6017, Col. 2, first paragraph). Thus, one of ordinary skill in the art, with Blann et al. and Takagi et al. in hand, would not conclude that vWF is not a causative factor in atherosclerosis and related diseases.

Thrombus formation is a key event in the origin and progression of atherosclerosis (Blann et al. p. 10, first line). Mature vWF promotes collagen-platelet interaction and subsequently thrombus formation (see Takagi et al. p. 6018, Col. 2, 2nd paragraph) and is found at highest concentrations in severe atherosclerosis (Blann et al. (p. 12, Col. 1, 2nd paragraph). Takagi et al. found that pp-vWF effectively causes collagen to lose its platelet aggregation activity (Takagi et al. (Col. 2, beginning at line 10, 2nd paragraph). Thus, one of ordinary skill in the art would have had a reasonable expectation of success in using pp-vWF to counteract the platelet aggregation activities

of vWF using pp-vWF since Takagi et al. provides evidence that pp-vWF has that activity. Blann et al. suggests that agents that lower vWF concentration might be useful in the treatment of atherosclerosis and related diseases and Takagi et al. teaches that pp-vWF counteracts mature vWF. Applicants contend that the examiner has not considered that Blann et al. suggest future studies rather than suggesting that new treatments would be successful. However, as explained in the previous Office Action, all that is required is a motivation to make the composition claimed. The suggestion of Blann et al. and the knowledge of the teachings of Takagi et al., at the very least, would have motivated one of ordinary skill in the art to characterize the in vivo activities of pp-vWF as a potential therapeutic agent. Pursuing such research and trials, one of ordinary skill in the art would have wanted to obtain the most highly purified preparations of pp-vWF and would have included steps of eliminating any viral proteins that would contaminate the preparation and potentially cause erroneous results. In other words, in testing a potential therapeutic agent, one of ordinary skill in the art would have wanted to use a preparation that was representative of that that would be used in therapy. One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of obtaining highly pure preparations of pp-vWF since purification methods for pp-vWF were well known (as evidenced by Takagi et al.) and since virus removal methods were well known (as evidenced by EP 0 131 740). Therefore, in the present case, the combined references provide 1) methodology to make the claimed product (see Takagi et al. and EP 0 131 740), 2) a suggestion to use

the claimed product as a pharmaceutical (see Takagi and Blann et al.), and 3) evidence suggesting such use would be successful (see Takagi et al. and Blann et al.).

In response to applicant's argument that the inventors recognized a pharmacological function of the vWF propeptide not taught or suggested in the cited references, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The rejection is maintained.

Claim Rejections - 35 USC § 112

Claims 68, 69, 77 and 78 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A pharmaceutical preparation for treating blood coagulation disorders wherein the preparation comprises at least 10 nM or at least 100 nM pro-vWF is not enabled by the disclosure.

The rejection is maintained for the reasons cited in the Office Action mailed January 12, 2004.

As stated in the previous Office Action, the Specification does not provide guidance for a method of purification of pro-vWF and there is no evidence that such purification was routine in the art. Applicants argue that one of skill in the art could have used the teachings of Fischer et al. (FEBS Lett. 351: 345 (1994) and Megan (Thromb. Haemost. 59: 364 (1998) in the purification of pro-vWF. This argument has been

considered but is not deemed persuasive because Fischer et al. and Megan et al. do not appear to teach a method of purifying pro-vWF. Fischer et al. teach a method of expressing full-length vWF in CHO cells and its subsequent isolation. Megan et al. teach a process for immunopurification of FVIII/vWF complex from plasma. These references do not teach that the processes taught therein could yield at least 10 nM pro-vWF. Thus, since Applicants state that the pro-vWF is highly labile (see Paper No. 19, p. 5) and there is no evidence of art prior to the invention that teaches the purification of pro-vWF, such a teaching would have been required in order for one of skill in the art to make the pro-vWF. The rejection is maintained. It is noted that Claims 68 and 69 were added to this rejection due to the amendment and they are rejected for the same reasons discussed above and in the previous Office Action.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 73 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 73 depends from a cancelled claim therefore the metes and bounds of the claim are unclear. Correction is required.

Claim Objections

Claims 35-37 41 and 66 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

HS

Holly Schnizer
September 22, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER